A Phase 1 trial to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple oral doses of AS-0871 and to evaluate the relative bioavailability and the food effect of new oral formulations of AS-0871 in healthy subjects.

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In this study we will investigate how safe the new compound AS-0871 is and how well it is tolerated when it is used by healthy participants. We will also investigate how quickly and to what extent AS-0871 is absorbed, transported, and eliminated...

Ethical review	Approved WMO
Status	Completed
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON53402

Source
ToetsingOnline

Brief title
Safety, PK and PD study of AS-0871 in healthy subjects

Condition

- Allergic conditions

Synonym
hives and rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Carna Biosciences, Inc.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: AS-0871, Healthy subjects, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

Part 1:

To explore the effect of food on the plasma PK of AS-0871, formulated as AS-0871/DES capsules, following single-dose oral administration in healthy subjects.

Part 1a:

To explore the effect of food on the plasma PK of AS-0871, formulated as AS-0871/ASD tablets, following single-dose oral administration in healthy subjects.

Part 2:

To evaluate the safety and tolerability of AS-0871 following 14-day multiple-dose oral administration in healthy subjects.

Secondary outcome

Part 1:

To evaluate the relative bioavailability of AS-0871, formulated as AS-0871/DES

capsules, under fasted and fed conditions in healthy subjects in comparison with the AS-0871 oral SDD suspension previously tested in trial C0871101.
To evaluate the safety and tolerability of AS-0871, formulated as AS-0871/DES capsules, following single-dose oral administration under fasted and fed conditions in healthy subjects.

Part 1a:

To evaluate the relative bioavailability of AS-0871, formulated as AS-0871/ASD tablets, under fasted and fed conditions in healthy subjects in comparison with the AS-0871 oral SDD suspension previously tested in trial C0871101.
To evaluate the safety and tolerability of AS-0871, formulated as AS-0871/ASD tablets, following single-dose oral administration under fasted and fed conditions in healthy subjects.

Part 2:

To evaluate the plasma PK of AS-0871 following 14-day multiple-dose oral administration in healthy subjects.
To evaluate the PD (basophil response) of AS-0871 (in blood) following 14-day multiple-dose oral administration in healthy subjects.
To perform correlation analysis of plasma concentration - PD (basophil response) of AS-0871.

Study description

Background summary

AS-0871 is a new compound that may potentially be used for the treatment of allergic and autoimmune disorders such as hives and rheumatoid arthritis. AS-0871 inhibits the activity of white blood cells called basophils, which may be overactive in certain allergic diseases. AS-0871 also has an effect on cells called B-cells. B-cells are part of the immune system and play a central role in the volunteers body ability to defend itself against pathogens. In certain types of diseases of the immune system, the B-cells may not be working properly or they may be overactive. AS-0871 is intended to slow down the B-cell activity and may therefore potentially be used for the treatment of these diseases.

Study objective

In this study we will investigate how safe the new compound AS-0871 is and how well it is tolerated when it is used by healthy participants.

We will also investigate how quickly and to what extent AS-0871 is absorbed, transported, and eliminated from the body (this is called pharmacokinetics).

Part 1:
In addition, we will look at the effect of food on how the body handles AS-0871 in capsules. To study this, the study compound will be given once with and once without food.

Part 1a:
In addition, we will look at the effect of food on how the body handles AS-0871 in tablets. To study this, the study compound will be given once with and once without food.

Part 2:
In addition, we will look at the effect of AS-0871 in tablets on white blood cells and we check for any breakdown products (metabolites) of AS-0871.

We will compare the effects of AS-0871 with the effects of a placebo.

AS-0871 has been given to humans before in a previous clinical study. It has also been extensively tested in the laboratory and on animals. AS-0871 will be tested at various dose levels in this study.

Study design

Part 1:

The study will take approximately 6 weeks from the screening until the follow-up visit.
For the study, it is necessary that the volunteer stays in the research center for 2 periods of 5 days (4 nights). This will be followed by a follow-up visit after the second period.

The volunteer will receive a dose of the study compound once per period, so two times in total. Each dose will be 300 milligram (mg) AS-0871. Each capsule is 50 mg, so, in total, 6 capsules per dosing.

Part 1a:
The study will take approximately 6 weeks from the screening until the follow-up visit.
For the study, it is necessary that the volunteer stays in the research center for 2 periods of 5 days (4 nights). This will be followed by a follow-up visit after the second period.

The volunteer will receive a dose of the study compound once per period, so two times in total. Each dose will be 300 milligram (mg) AS-0871. Each tablet is 50 mg, so, in total, 6 tablets per dosing.

Part 2:
The study will take a maximum of 7 weeks weeks from the screening until the follow-up visit.
For the study, it is necessary that the volunteer stays in the research center for 18 days (17 nights). Afterwards the volunteer will come back to the research center for the follow-up visit.

The volunteer will receive a dose of the study compound twice daily for 13 days, with one additional dose on Day 14. This means that the volunteer will have 27 doses in total. There will be 12 hours between each dosing. The dose that the volunteer will receive depends on which group he is in. The study compound will be given as capsules. Each capsule contains 50 milligram AS-0871 or placebo. The number of capsules the volunteer has to take depends on which group he is in.

Intervention

The volunteer will be given AS-0871 (Part 2: or placebo) as oral capsules (part 1) or tablets (part 1a and 2) with 240 milliliters (mL) of (tap) water. Intake of the study compound should occur within 6 minutes. More water (up to 160 mL for a total of 400 mL) may be used and more time (up to 4 minutes for a total of 10 minutes) may be given if needed.

Part 1:
Participants will receive the study compound as capsules with a breakfast in one period and without breakfast in the other period. The order in which this

will occur depends on what group the volunteer is in. In one period the volunteer will receive a high fat breakfast with a standard composition, which must be started exactly on time and must be finished within 20 minutes.

Part 1a:
Participants will receive the study compound as tablets with a breakfast in one period and without breakfast in the other period. The order in which this will occur depends on what group the volunteer is in. In one period the volunteer will receive a high fat breakfast with a standard composition, which must be started exactly on time and must be finished within 20 minutes.

Part 2:
Whether the study compound as tablets will be given after fasting or after food will be decided based on the results of Part 1 and Part 1a of this study (which examines the effect of food on the absorption of AS-0871).

Study burden and risks

Possible side effects:
The study compound may cause side effects.

One study has been completed in which a total of 16 healthy adult male and female participants received at least 1 single dose of AS-0871. Doses of 5, 25, 100, 300, 600, and 900 mg were tested in this study. Overall, single doses of AS-0871 up to 900 mg after fasting and at 300 mg after food were well tolerated. Below you can find an overview of side effects that were considered to be related to the treatment with AS-0871. They were all of mild intensity and resolved during the study.
- Headache (7 participants)
- Nausea (6 participants)
- Vomiting (3 participants)
- Diarrhea (2 participants)
- Fever (2 participants)
- Fatigue (2 participants)
- Flatulence (1 participant)
- Throat irritation (1 participant)
- Taste disorder (1 participant)
- Malaise (1 participant)
- Feeling hot (1 participant)
- Excessive sweating (1 participant)

No relevant abnormalities were observed in any of the laboratory measurements, ECGs, vital signs, or physical examinations. In one subject, a transient mild elevation of liver enzymes was observed at 600 and 900 mg of AS 0871. This was not considered clinically relevant (not of practical importance).

The occurrence of headache and gastrointestinal disorders have also been

reported for compounds that are similar to AS-0871, like acalabrutinib.

Acalabrutinib is a marketed compound that has a similar mechanism of action as AS-0871. The safety of acalabrutinib was tested in different doses in 59 healthy volunteers. Of the 59 healthy volunteers, 16 had 1 or more side effect during the study. In total, 3 side effects were assessed to be related to acalabrutinib. These were constipation, somnolence, and feeling cold and were generally mild. No effect of acalabrutinib was observed on laboratory values, physical examinations, vital signs, or ECG measurements.

Based on experience with other compounds that have a similar mode of action as AS-0871, we will be paying attention for bleeding or bruising. Results of an investigation with AS-0871 in dogs have become available in November 2022. In this dog study, the animals were treated for 13 weeks with different doses of AS-0871. In one animal, given a relatively high dose level, a small spot of bleeding was observed in the heart muscle. Compared with the doses planned to be given in this part of the trial, there are still sufficient safety margins.
For the planned 50 mg dose level (Group B), the safety margin is 8.4-fold, for the planned 100 mg dose level (Group C), the safety margin is 4.2-fold, and for the planned 200 mg dose level (Group D), the safety margin is 2.1-fold. The exact relationship of the finding with the dosing of AS-0871 is not clear yet. Since the animals were dosed for 13 weeks twice daily, it is expected that the risk for participants in this trial with 14 days of dosing with AS-0871 is still very low. In addition, extra safety measures are implemented during your stay in the research center with telemetry to monitor your heart activity and clotting measurements to monitor these blood parameters in more detail.

The study compound may also have (serious) side effects that are still unknown. In addition to unknown side effects, there is a (small) chance that an allergic reaction will occur. This can be caused by the study compound or other ingredients that are used to prepare the formulation.

Possible discomforts:
Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula (a tube in a vein in the arm) can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about part 1: 106 milliliters, part 1a: 130 milliliters, part 2: 319 milliliters of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the

amount indicated above.

Heart tracing
To make a heart tracing, electrodes (small, plastic patches) will be placed on the arms, chest and legs of the volunteers. (Part 2: To monitor the volunteers heart activity over a longer period, electrodes (small, plastic patches) will be placed on the chest and abdomen). Prolonged use of these electrodes can cause skin irritation (rash and itching), but the test itself is harmless.

Meals/Fasting
Part 1: The high-fat breakfast is a big breakfast containing eg, 2 fried eggs, fried potatoes and bacon. The volunteer must consume the whole breakfast within 20 minutes. It can be difficult to consume the entire breakfast, particularly for light eaters .

If the volunteer has to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Coronavirus test
Samples for the coronavirus test will be taken from the back of nose and throat of the volunteer using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the volunteers throat may cause the volunteer to gag. When the sample is taken from the back of the nose of the volunteer, the volunteer may experience a stinging sensation and the eyes of the volunteers may become watery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Must have signed an ICF prior to screening, indicating that he/she understands the purpose of, and procedures required for, the trial, and indicating that he/she is willing to participate in the trial.
2. Healthy males or females of non-childbearing potential, between 18 and 64 years of age, inclusive, at screening.
3. Body mass index (BMI) between 18.0 and 30.0 kg/m2, inclusive, at screening.
4. Good physical and mental health as established by medical history, physical examination, ECG, and vital signs (including temporal body temperature) recording, and results of biochemistry, coagulation (Part 2 only), hematology, and urinalysis tests during screening as judged by the investigator.
5. Non-smoker/non-user of nicotine-containing products for at least 3 months prior to screening, to be confirmed by a urine cotinine test at screening and on Day -1 (of the first treatment period, as applicable).

Further criteria apply, see protocol.

Exclusion criteria

1. History of or current clinically significant medical illness including (but not limited to) gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, neoplastic, hematologic (including coagulation disorders), or infectious disease, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the trial results.
2. Clinically relevant abnormal values for hematology, coagulation (Part 2 only), biochemistry, or urinalysis at screening or on Day -1 (of the first treatment period, as applicable), as judged by the investigator.

3. Values of hepatic aminotransferase (ALT and/or AST) >1.5xULN at screening or on Day -1 (of the first treatment period, as applicable).
4. Values of GGT and/or ALP >1.25xULN at screening or on Day -1 (of the first treatment period, as applicable).
5. Values of total cholesterol and LDL cholesterol >1.25xULN at screening or on Day -1 (of the first treatment period, as applicable).

Further criteria apply, see protocol.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-12-2021
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	18-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2021

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	15-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-003339-27-NL
CCMO	NL79593.056.21

Study results

Date completed:	17-04-2023
Results posted:	11-03-2024

First publication
31-10-2023